Figure 1

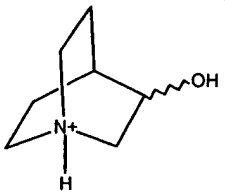
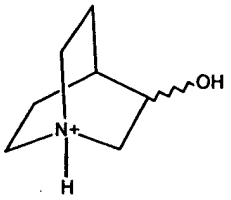
Allosteric Effector	Structure or Name
ICP6	Nona-cyclohexylammonium tri-sodium inositol hexaphosphate
IC2P1	Bis-dicyclohexylammonium deca-sodium inositol hexaphosphate
IC2P2	Octa-dicyclohexylammonium inositol hexaphosphate
SV42	Hexa-dibenzylmethylammonium inositol hexaphosphate
SV44	 Hepta inositol hexaphosphate
SV45	 Dodeca- inositol hexaphosphate
SV46	Nona-piperidinium inositol hexaphosphate

Figure 2

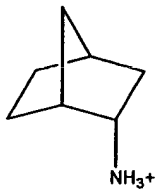
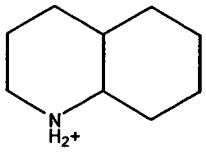
Allosteric Effector	Structure or Name
SV47	Penta-H_3N-Phe-OMe inositol hexaphosphate
SV48	Nona-H_3N-Phe-OMe inositol hexaphosphate
SV51	Hexa-1-indanylammonium inositol hexaphosphate
SV52	 Hepta- NH_3^+ inositol hexaphosphate
SV53	 Nona- inositol hexaphosphate
SV55	Hepta-H_3N-Phe-OEt inositol hexaphosphate
SV56	Hexa-H_3N-Phe-OEt inositol hexaphosphate
SV57	Octa-H_3N-*sec*-Leu-Ot-Bu inositol hexaphosphate
SV58	Dodeca-diisopropylammonium inositol hexaphosphate
SV59	Octa-H_2N-Pro-Ot-Bu inositol hexaphosphate

Figure 3

Allosteric Effector	Structure or Name
SV68	Deca-H_3N-Tyr-OEt inositol hexaphosphate
SV71	Undeca-4-t-butylcyclohexylammonium inositol hexaphosphate
SV73	Tetra-cyclohexyl-1,2-bis-ammonium inositol hexaphosphate
SV74	Undeca-adamantylammonium inositol hexaphosphate
SV75	Nona-cycloheptylammonium inositol hexaphosphate
SV78	Undeca-cyclopentylammonium inositol hexaphosphate
SV80	Hepta-H_3N-Try-OEt inositol hexaphosphate
SV81	Undeca-cyclohexylammonium inositol hexaphosphate
SV99	Hexa-dimethylcyclohexylammonium inositol hexaphosphate
SV115	Nona-hexylammonium inositol hexaphosphate
SV131	Undeca-cyclooctanylammonium inositol hexaphosphate
SV135	Nona-octylammonium inositol hexaphosphate
IP12	Hepta-tributylammonium inositol hexaphosphate

Figure 4

Cyclic Primary Amines

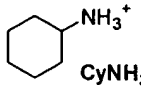
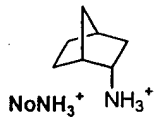
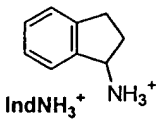
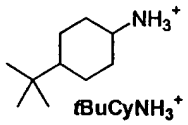
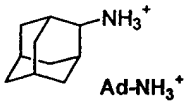
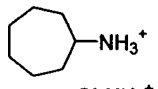
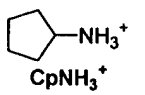
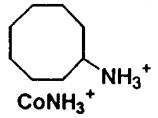
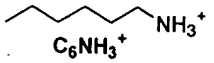
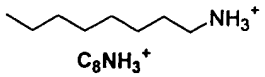
Reference	Counter-cation	Number	Mol. Formula	Mol. Weight ($g.mol^{-1}$)
ICP_1		**1** Bu_3NH^+ **6** $CyNH_3^+$ **5** Na^+	$C_{54}H_{118}O_{24}N_7P_6Na_5$	1550.37
ICP_2		**9** $CyNH_3^+$ **3** Na^+	$C_{60}H_{130}O_{24}N_9P_6Na_3$	1616.57
ICP_3	 $CyNH_3^+$	**9** $CyNH_3^+$ **3** Na^+	$C_{60}H_{130}O_{24}N_9P_6Na_3$	1616.57
ICP_4		**11** $CyNH_3^+$ **1** Na^+	$C_{72}H_{160}O_{24}N_{11}P_6Na_1$	1772.97
ICP_5		**9** $CyNH_3^+$ **3** Na^+	$C_{60}H_{130}O_{24}N_9P_6Na_3$	1616.57
ICP_6		**9** $CyNH_3^+$ **3** Na^+	$C_{60}H_{130}O_{24}N_9P_6Na_3$	1616.57
SV52	 $NoNH_3^+$ NH_3^+	**7** $No\text{-}NH_3^+$	$C_{55}H_{104}O_{24}N_7P_6$	1433.32
SV51	 $IndNH_3^+$ NH_3^+	**6** $Ind\text{-}NH_3^+$	$C_{60}H_{84}O_{24}N_6P_6$	1459.21 $H_{5.80}N_{5.76}C_{49..39}$
SV69	 $tBuCyNH_3^+$	**11** tBuCy-NH_3^+	$C_{116}H_{249}O_{24}N_{11}P_6$	2368.18 $H_{10.6}C_{58.83}N_{6.51}$
SV71		**7** tBuCy-NH_3^+	$C_{76}H_{165}O_{40}N_8P_6$	1747.03 $H_{9.52}C_{52.26}N_{5.61}$
SV74	 $Ad\text{-}NH_3^+$	**11** $Ad\text{-}NH_3^+$	$C_{116}H_{194}O_{24}N_{11}P_6$	2312.74 $H_{8.46}C_{60.24}N_{6.66}$
SV75	 $ChNH_3^+$	**9** $Ch\text{-}NH_3^+$	$C_{69}H_{153}O_{24}N_9P_6$	1819.52 $H_{5.98}C_{47.53}N_{4.62}$
SV76	 $CpNH_3^+$	**11** $Cp\text{-}NH_3^+$	$C_{61}H_{139}O_{24}N_{11}P_6$	1596.69 $H_{8.77}C_{45.89}N_{9.65}$
SV131	 $CoNH_3^+$	**11** $Co\text{-}NH_3^+$	$C_{94}H_{205}O_{24}N_{11}P_6$	2059.58
SV220		**10** $Co\text{-}NH_3^+$	$C_{86}H_{188}O_{24}N_{10}P_6$	1932.35

Figure 5

Acyclic Primary Amines

SV112		7 $C_6NH_3^+$	$C_{48}H_{123}O_{24}N_7P_6$	1368.39
SV115		9 $C_6NH_3^+$	$C_{60}H_{153}O_{24}N_9P_6$	1570.78
SV135		9 $C_8NH_3^+$	$C_{78}H_{189}O_{24}N_9P_6$	1821

Amino-acids

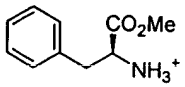
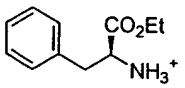
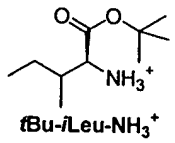
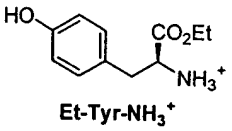
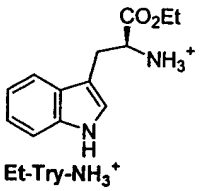
SV47		5 Me-PheAla-NH_3^+	$C_{56}H_{76}O_{34}N_5P_6$	1549.08
SV48		9 Me-PheAla-NH_3^+	$C_{96}H_{132}O_{42}N_9P_6$	2270.00
SV55		7 Et-PheAla-NH_3^+	$C_{83}H_{123}O_{38}N_7P_6$	2012.77 $H_{6.16}N_{4.87}C_{49..53}$
SV56		6 Et-PheAla-NH_3^+	$C_{72}H_{108}O_{36}N_6P_6$	1819.52 $H_{5.98}C_{47.53}N_{4.62}$
SV57		8 *t*Bu-*i*Leu-NH_3^+	$C_{78}H_{154}O_{40}N_8P_6$	1819.52 $H_{5.98}C_{47.53}N_{4.62}$
SV68		10 Et-Tyr-NH_3^+	$C_{116}H_{168}O_{54}N_{10}P_6$	2752.51 $H_{6.15}C_{50.62}N_{5.09}$
SV80		7 Et-Try-NH_3^+	$C_{97}H_{130}O_{38}N_{14}P_6$	2286.03

Figure 6

Secondary Amines

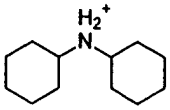
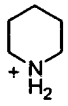
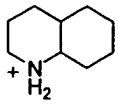
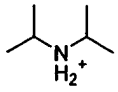
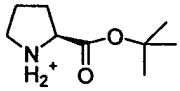
Reference	Counter-cation	Number	Mol. Formula	Mol. Weight ($g.mol^{-1}$)
$IC2P_1$	 $Cy_2NH_2^+$	**2** $Cy_2NH_3^+$ **10** Na^+	$C_{30}H_{54}O_{24}N_2P_6Na_{10}$	1242.50
$IC2P_2$		**8** $Cy_2NH_3^+$	$C_{102}H_{202}O_{24}N_8P_6$	2110.63
SV46	$PiNH_2^+$ 	**9** $PiNH_2^+$	$C_{51}H_{117}O_{24}N_9P_6$	1426.39
SV53	 $DHQ\text{-}NH_2^+$	**9** $PiNH_2^+$	$C_{87}H_{171}O_{24}N_9P_6$	1913.22 $H_{9.01}C_{54.62}N_{6.59}$
SV58	 $iPr_2\text{-}NH_2^+$	**12** $iPr_2NH_2^+$	$C_{78}H_{198}O_{24}N_{12}P_6$	1874.36 $H_{10.65}C_{49.98}N_{8.97}$
SV59	 $tBu\text{-}Pro\text{-}NH_2^+$	**8** $tBu\text{-}ProNH_2^+$	$C_{78}H_{154}O_{40}N_8P_6$	1874.36 $H_{7.65}C_{46.15}N_{5.52}$

Figure 7

Tertiary Amines

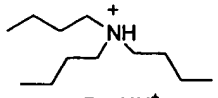
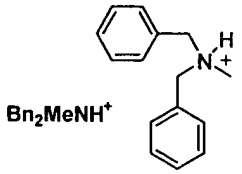
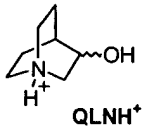
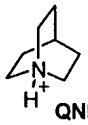
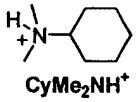
Reference	Counter-cation	Number	Mol. Formula	Mol. Weight ($g.mol^{-1}$)
IP_{12}	 Bu_3NH^+	7 Bu_3NH^+ 5 Na^+	$C_{90}H_{202}O_{24}N_7P_6Na_6$	2067.43
SV42	 Bn_2MeNH^+	6 Bn_2MeNH^+	$C_{96}H_{120}O_{24}N_6P_6$	1550.66 $H_{6.27}C_{59.81}N_{4.36}$
SV44	 $QLNH^+$	7 $QLNH^+$	$C_{55}H_{109}O_{31}N_7P_6$	1550.35
SV45	 QNH^+	12 QNH^+	$C_{90}H_{174}O_{24}N_{12}P_6$	1994.30 $H_{8.79}C_{54.2}N_{8.43}$
SV99	 $CyMe_2NH^+$	6 $CyMe_2NH^+$	$C_{54}H_{114}O_{24}N_6P_6$	1417.38 $H_{8.11}C_{45.76}N_{5.93}$

Figure 8

Diamines

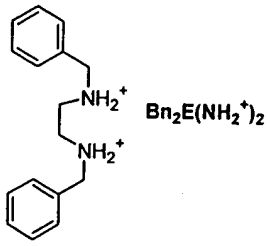
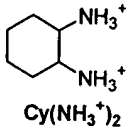
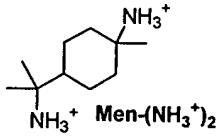
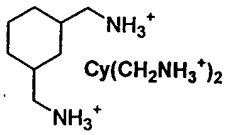
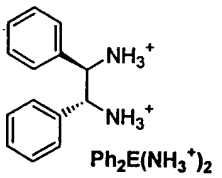
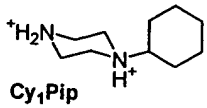
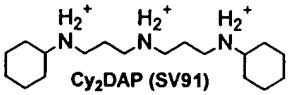
Reference	Counter-cation	Number	Mol. Formula	Mol. Weight ($g.mol^{-1}$)
SV72	 $Bn_2E(NH_2^+)_2$	5 $Bn_2E(NH^+)_2$	$C_{86}H_{108}O_{24}N_{10}P_6$	1851.71 $H_{5.88}C_{55.78}N_{7.56}$
SV76		4 $Bn_2E(NH^+)_2$	$C_{70}H_{88}O_{24}N_8P_6$	1611.36 $H_{5.5}C_{52.18}N_{6.95}$
SV73	 $Cy(NH_3^+)_2$	4 $Cy(NH_3^+)_2$	$C_{30}H_{68}O_{24}N_8P_6$	1110.76
SV92		5 $Cy(NH_3^+)_2$	$C_{36}H_{88}O_{24}N_{10}P_6$	1231.00
SV89	 $Men\text{-}(NH_3^+)_2$	8 $Men\text{-}(NH_3^+)_2$	$C_{86}H_{228}O_{24}N_{16}P_6$	2056.71
SV94	 $Cy(CH_2NH_3^+)_2$	5 $Cy\text{-}(CH_2NH_3^+)_2$	$C_{46}H_{108}O_{24}N_{10}P_6$	1371.27
SV95	 $Ph_2E(NH_3^+)_2$	5 $Ph_2E(NH_3^+)_2$	$C_{76}H_{98}O_{24}N_{10}P_6$	1721.52
SV97	 Cy_1Pip	9 Cy_1Pip	$C_{96}H_{192}O_{24}N_{10}P_6$	2056.50

Figure 9

Triamines

Reference	Counter-cation	Number	Mol. Formula	Mol. Weight ($g.mol^{-1}$)
SV101	 Cy_2DAP (SV91)	2 Cy_2DAP	$C_{42}H_{92}O_{24}N_6P_6$	1251.07
SV120		3.6 Cy_2DAP	$C_{71}H_{145}O_{24}N_{11}P_6$	1722.85

Tetra-amines

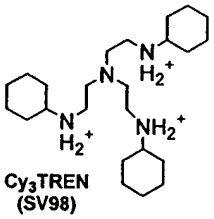
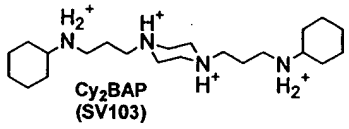
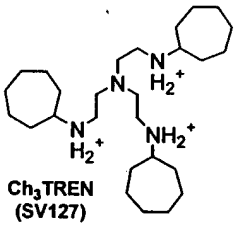
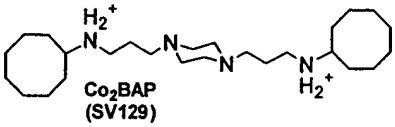
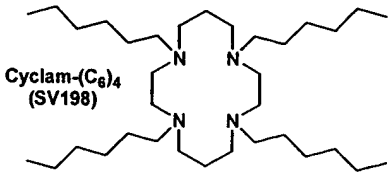
Ref	Counter-cation	Number	Mol. Formula	Mol. Weight ($g.mol^{-1}$)
SV102	 Cy_3TREN (SV98)	3 Cy_3TREN	$C_{78}H_{162}O_{24}N_{12}P_6$	1838.07
SV106	 Cy_2BAP (SV103)	4 Cy_2BAP	$C_{94}H_{194}O_{24}N_{16}P_6$	2118.53
SV137	 Ch_3TREN (SV127)	2 Ch_3TREN	$C_{60}H_{120}O_{24}N_8P_6$	1523.51
SV141	 Co_2BAP (SV129)	3 Co_2BAP	$C_{84}H_{174}O_{24}N_{12}P_6$	1922.2
SV202	 Cyclam-$(C_6)_4$ (SV198)	2 Cyclam-$(C_6)_4$	$C_{74}H_{162}O_{24}N_8P_6$	1733.99

Figure 10

Hexa-amines

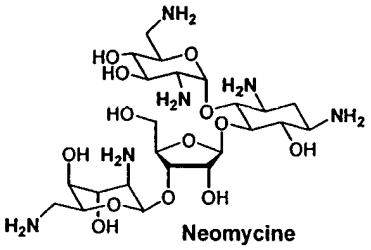
Ref	Counter-cation	Number	Mol. Formula	Mol. Weight ($g.mol^{-1}$)
SV216	 Neomycine	1 Neomycin/IHP	$C_{29}H_{64}O_{37}N_6P_6$	1274.69
SV217		2 Neomycin/IHP	$C_{52}H_{110}O_{50}N_{12}P_6$	1889.35

Figure 11 Partition coefficients of IHP ammonium salts (at 30 mM).

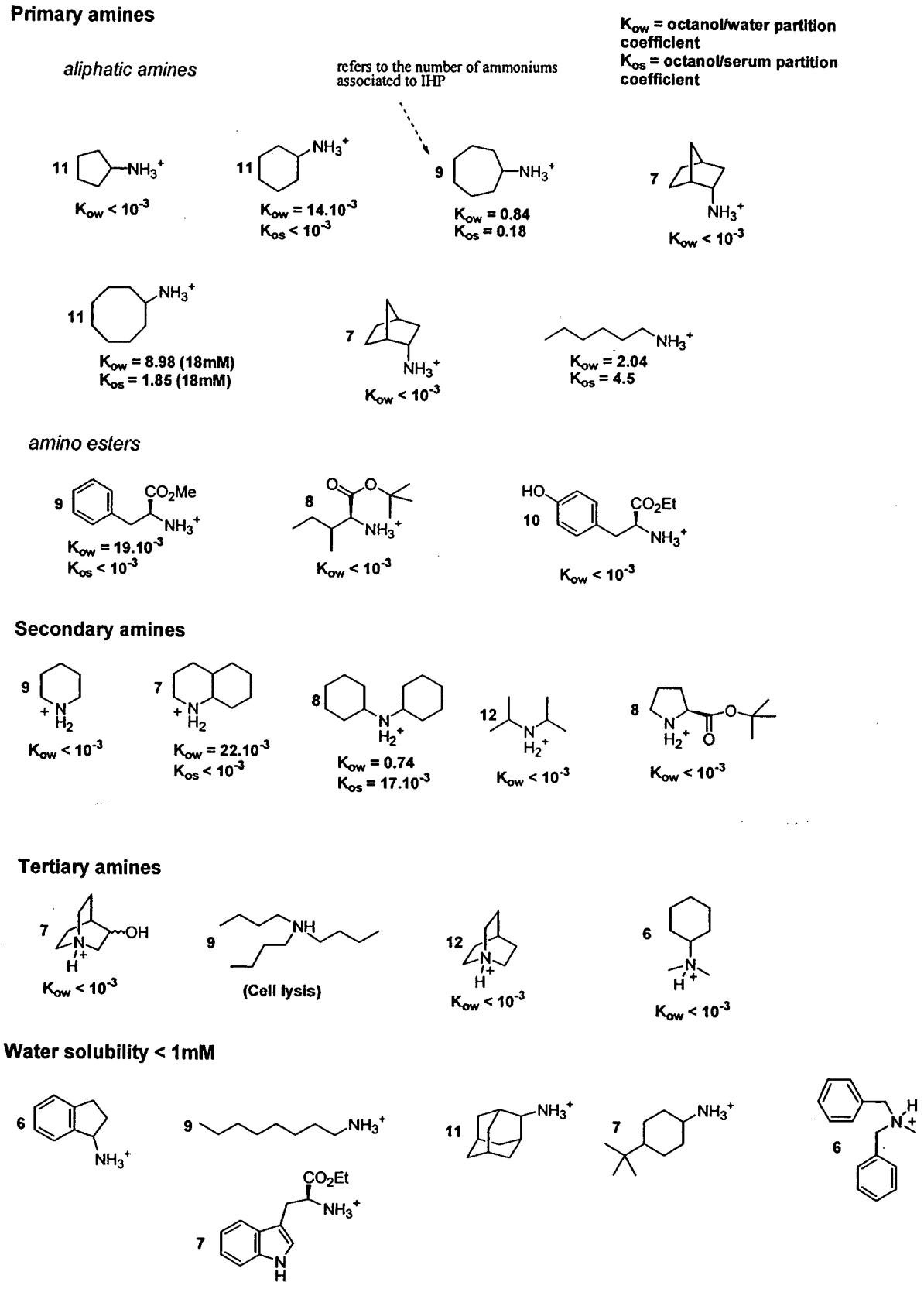
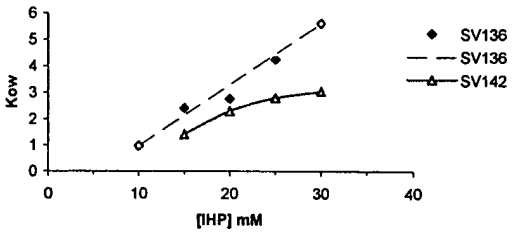
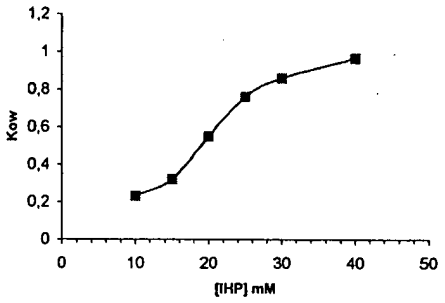


Figure 12



Experiments SV136 and SV142.

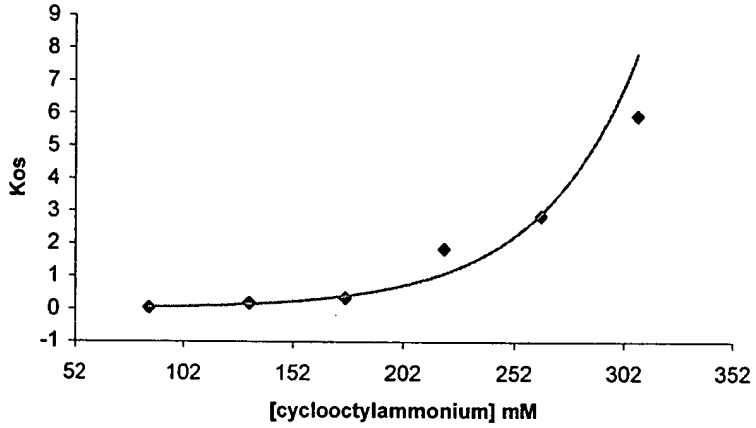
Compound **SV131** (IHP, 11 cyclooctylammonium) was dissolved in 1-octanol at various concentrations and agitated with an equal volume of artificial serum (SV136) or human serum (SV142).



Experiment SV134.

Compound **SV75** (IHP, 9 cycloheptylammonium) was dissolved in octanol at various concentrations and agitated with an equal volume of water.

Figure 13



IHP uptake in 1-octanol by cyclooctylammonium ions. IHP, dodecasodium form, was dissolved in human serum ([IHP] = 22 mM, pH = 7.4). Each samples were agitated 2 days with an equal volume of octanolic solution of cyclooctylamine,HCl at different concentrations. Partition coefficients K_{OS} were measured by ^{31}P-NMR.

Figure 14 P_{50} values obtained from O_2-dissociation curves using whole blood.

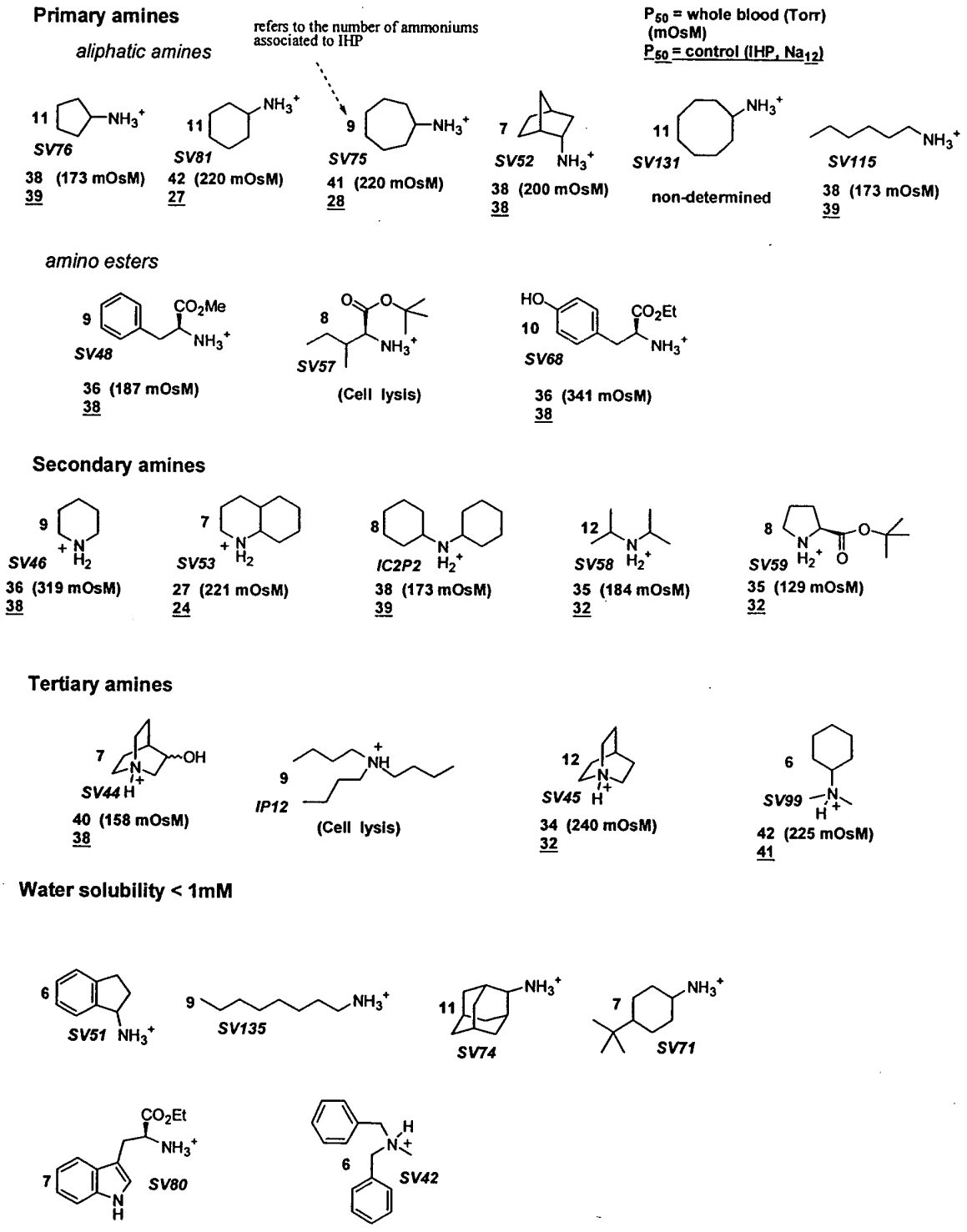


Figure 15

Effector	P50 CONTROL WB mmHg	P50 EFF: WB mmHg	CONC. EFF mM	CONC EFF:WB mM	OSMOL. EFF mOsM	pH EFF.	pH EFF:WB or EFF:*fHb*	Volume Ratio EFF:WB
HBS+					310		7.22	
***f*Hb in HBS+**							7.22	
ICP6								
WB	27.5	39	30	22	220		7.23	1:0.375
WB	27.5	27.5	30	22	312		7.2	1:0.375
WB	27.5	31	30	22	262		7.21	1:0.375
WB	27.5	27.5	60	44	318		7.32	1:1.5
*f*Hb	16	43.5					7.18	0.25 μM EFF
IC2P1								
WB	38.5	39.5	30	22	160		6.04	1:0.375
WB	38.5	39.5	30	22	160		6.03	1:0.375

*f*Hb = free hemoglobin; WB = whole blood; EFF = effector.

Figure 16

Effector	P50 CONTROL WB mmHg	P50 EFF: WB mmHg	CONC. EFF mM	CONC EFF:WB mM	OSMOL. EFF mOsM	pH EFF.	pH EFF:WB or EFF:*fHb*	Volume Ratio EFF:WB
IC2P2								
WB	38	41	30	22	302	7.44	6.94	1:0.375
WB	38	39.5	30	22	323		7.21	1:0.375
*f*Hb	16.5	41.5					7.17	0.25 μM EFF
SV44								
WB	37.5	40	30	22	158		7.23	1:0.375
WB	37.5	37.5	30	12	315		6.98	1:1.5
*f*Hb	16	42.5					7.17	0.25 μM EFF
SV46								
WB	38.5	36	30	12	319		7.13	1:1.5
*f*Hb	16	42						0.25 μM EFF
SV47								
WB	38.5	38.5	30	22	173		6.93	1:0.375
WB	38.5	38.5	30	12	338		7.41	1:1.5
*f*Hb	16	45.5					7.11	0.25 μM EFF
SV48								
WB	38.5	36	30	22	187		6.88	1:0.375
WB	38.5	37	30	12	326		7.26	1:1.5
*f*Hb	16	48					7.1	0.25 μM EFF
SV51								
WB	25	28.5	30	22	220	7.67	7.36	1:0.375
WB	25	24.5	30	12	220	7.67		1:1.5
WB	24.5	27	30	12	220	7.51	6.99	1:1.5
WB	28.5	28.5	30	12	344	7.64	7.27	1:1.5
*f*Hb	16	44					7.19	0.25 μM EFF
SV52								
WB	38.5	38.5	30	22	200		6.4	1:0.375
*f*Hb	16	45.5					7.15	0.25 μM EFF
SV53								
WB	24.5	27	30	12	221	7.12	6.6	1:1.5
WB	28.5	28.5	30	12	362	7.86	7.27	1:1.5
*f*Hb	16	43					7.18	0.25 μM EFF

*f*Hb = free hemoglobin; WB = whole blood; EFF = effector

Figure 17

Effector	P50 CONTROL WB mmHg	P50 EFF: WB mmHg	CONC. EFF mM	CONC EFF:WB mM	OSMOL. EFF mOsM	pH EFF.	pH EFF:WB or EFF:*fHb*	Volume Ratio EFF:WB
SV55								
WB	28.5	28.5	30	12	346	7.58	7.21	1:1.5
*f*Hb	16	48.5					7.15	0.25 µM EFF
SV56								
WB	28.5	28.5	30	12	325	7.35	7.36	1:1.5
*f*Hb	16	41					7.15	0.25 µM EFF
SV45								
WB	32.5	34.5	30	22	240	7.38		1:0.375
*f*Hb	16.5	45.5					7.18	0.25 µM EFF
SV57								
WB	32.5	Lysis	30	22	323	7.28		1:0.375
*f*Hb	16.5	43					7.16	0.25 µM EFF
SV58								
WB	32.5	35.6	30	22	184	7.41		1:0.375
*f*Hb	16.5	43					7.17	0.25 µM EFF
SV59								
WB	32.5	35.3	30	22	129	7.32		1:0.375
*f*Hb	16.5	41.5					7.16	0.25 µM EFF
SV68								
WB	38	36	30	12	341		7.38	1:1.5
*f*Hb	16.5	50					7.15	0.25 µM EFF
SV73								
WB	38	36	30	12	72		6.17	1:1.5
WB	38	36	30	12	335		7.31	1:1.5
WB	38	57	30	22	68		7.54	1:0.375
*f*Hb	16.5	43					7.2	0.25 µM EFF
SV75								
*f*Hb	16.5	45					7.2	0.25 µM EFF
SV78								
WB	38	36	30	12	309		7.3	1:1.5
*f*Hb	16.5	46					7.2	0.25 µM EFF
SV81								
WB	38	36	30	12	341		7.38	1:1.5
*f*Hb	16.5	44					7.2	0.25 µM EFF

*f*Hb = free hemoglobin; WB = whole blood; EFF = effector.

Figure 18

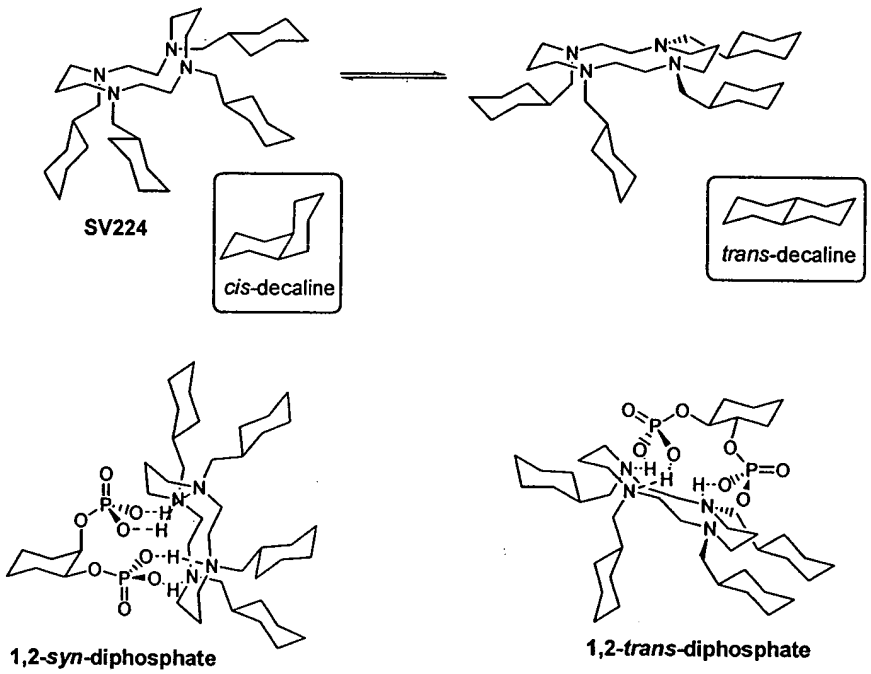
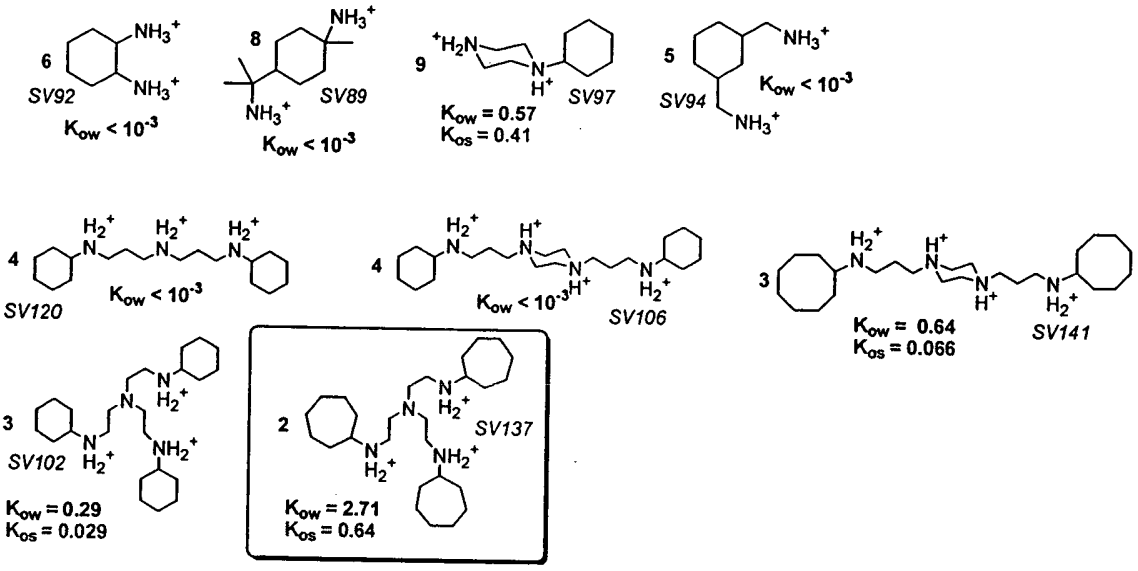

SV224
cis-decaline
trans-decaline
1,2-syn-diphosphate
1,2-trans-diphosphate

Figure 19

K_{ow} = octanol/water partition coefficient
K_{os} = octanol/serum partition coefficient

Polyamines



Water solubility < 1mM

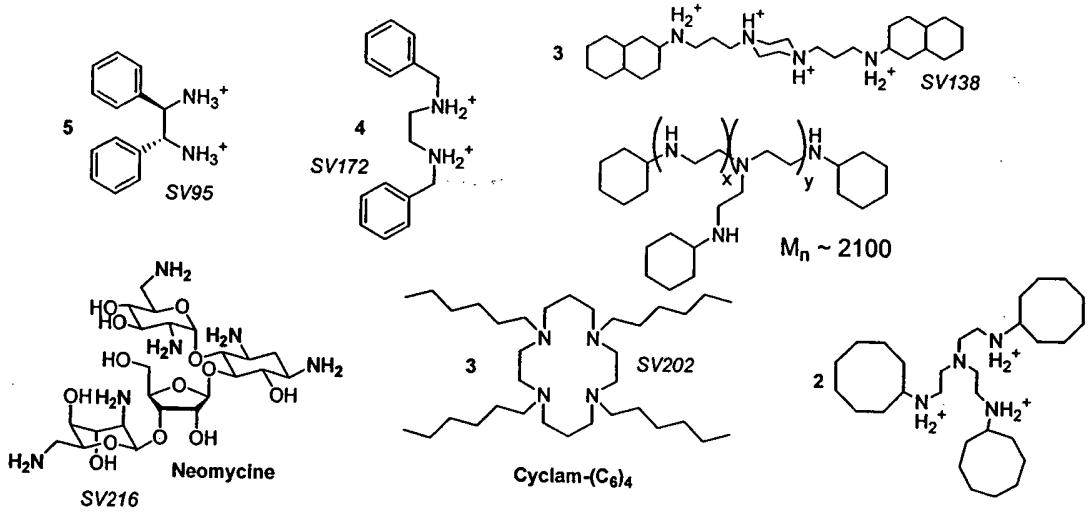
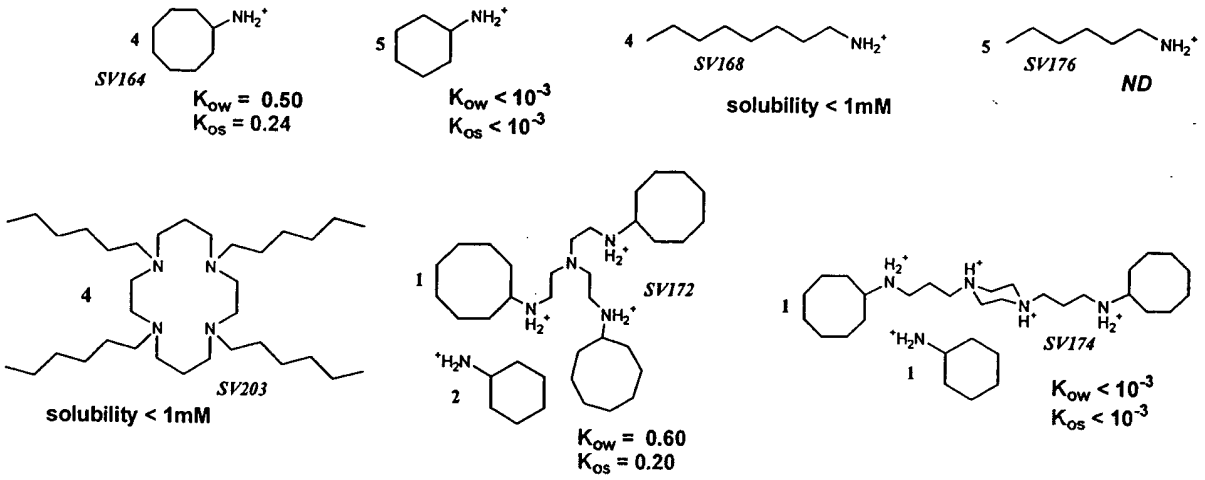


Figure 20


4
NH2+
SV164
Kow = 0.50
Kos = 0.24
5
NH2+
Kow < 10-3
Kos < 10-3
4
NH2+
SV168
solubility < 1mM
5
NH2+
SV176
ND
4
N
N
N
N
SV203
solubility < 1mM
1
N
N
N
H2+
NH2+
SV172
+H2N
2
Kow = 0.60
Kos = 0.20
1
H2+
N
H+
N
H+
N
H2+
SV174
+H2N
1
Kow < 10-3
Kos < 10-3